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## Development, validation and outcome of health-related quality of life questionnaires for food allergic patients

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*  
2009

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Flokstra-de Blok, B. M. J. (2009). *Development, validation and outcome of health-related quality of life questionnaires for food allergic patients*. s.n.

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# Chapter 9

**Summary, discussion and future perspectives**

This thesis deals with the development, validation and outcome of disease-specific health-related quality of life (HRQL) questionnaires for patients with food allergy. In this final chapter we provide a general summary of our findings and we will generally discuss these findings. Finally, recommendations for future study will be provided.

## **The impact of food allergy on HRQL**

Since no cure is available, having a food allergy implies being vigilant in numerous situations and setting involving food <sup>1,2</sup>. This need for allergen avoidance may have a considerable impact on daily life. For example, patients have to read labels of pre-packaged products, which may be time consuming and which may cause frustration when labels are insufficient for the needs of food allergic patients <sup>3</sup>. In addition, when eating outside the home, patients always need to ask beforehand whether the offered food contains the allergen that should be avoided, which may be experienced as embarrassing in social situations. However, despite all the effort it may cost to avoid allergens in food, success is not guaranteed <sup>4</sup>. There is always a chance of accidental exposure <sup>5</sup>. For example, when ingredients of pre-packaged products are changed or when the restaurant personnel or the host is not aware of the danger of cross-contamination of allergens in food <sup>6</sup>. Finally, when a severe allergic reaction occurs, prompt and accurate administration of epinephrine may be required which by itself may provoke anxiety about being able to respond adequately <sup>7</sup>. Therefore, food allergy may have a considerable impact on quality of life <sup>8</sup>.

## **Need for valid HRQL questionnaires for food allergic patients**

Although food allergy might have a considerable impact on quality of life, no valid disease-specific HRQL questionnaires were available to measure the impact of food allergy on the patient's quality of life at the beginning of this study (June 2005) (**chapter 2**). The only well-validated HRQL questionnaire for food allergy available at that time, was the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire <sup>9</sup>. This questionnaire is completed by parents and measures the parental burden of having a child with food allergy. Although being useful and well designed, this questionnaire is not able to measure the impact of food allergy on HRQL as experienced by the patients themselves. Therefore, there was a need for valid disease-specific HRQL questionnaires that could be self-administered by food allergic patients and in this thesis we describe the development and validation of

these questionnaires. In very young children one can only make use of the proxy ratings of parents. Therefore, in addition and concomitantly to the questionnaires developed in this thesis, a parent-administered questionnaire has been developed as well: the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) <sup>10</sup>.

## Development, validation and reliability of HRQL questionnaires for food allergic patients

We developed and validated three disease-specific HRQL questionnaires for children (8-12 years), adolescents (13-17 years) and adults (18 years and older) with food allergy (**chapters 3, 4 and 5**) and in addition we investigated the reliability of these three questionnaires (**chapter 6**).

The development phase started with the generation of items for the new questionnaires. The main sources for items were food allergic patients. In semi-structured interviews patients were asked about troublesome aspects of having a food allergy in daily life. In addition, we searched the literature on food allergy and asked clinical experts for additional items. When no important new items emerged, the item generation was considered as complete. This item generation phase was followed by the item reduction phase, in which the obtained long lists of items concerning food allergy were given to other groups of food allergic patients. These patients were asked to indicate whether an item was applicable to them and if so, to rate on a five-point scale how troublesome that particular item was. By following this method, also named as the clinical impact method, we could select the most important items for the questionnaires. This resulted in the following three questionnaires:

- Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF),
- Food Allergy Quality of Life Questionnaire - Teenager Form (FAQLQ-TF),
- Food Allergy Quality of Life Questionnaire - Adult Form (FAQLQ-AF).

The item reduction phase was followed by the cross-sectional validation, in which the newly developed questionnaires were investigated as to their validity. The FAQLQs, the Food Allergy Independent Measure (FAIM, which will be discussed later on) and a generic HRQL questionnaire were sent to other groups of food allergic patients. By calculating correlation coefficients between the FAQLQs and the FAIM we showed acceptable levels of construct validity for all three questionnaires and by calculating correlation coefficients between the FAQLQs and the generic HRQL questionnaire we showed acceptable levels of convergent and discriminant validity for all three questionnaires. Finally, in **chapter 6** we demonstrated, by administering the questionnaires two times to the same patients within a 10 to 14 day interval, that all three questionnaires showed good test-retest reliability. Such reliability measures are important to ensure that what the questionnaire is measuring is reproducible.

## Why three separate questionnaires for three different age groups?

Different issues relating to food allergy may have different impacts at different stages of life. For example, a food allergic child may face problems when treats are given at school, whereas a food allergic adult, for example, may face problems when eating in restaurants. In addition to such practical problems, also the psycho-social impact of food allergy may differ with age. Think for example of peer pressure which may play an important role in adolescence. Therefore, a single questionnaire cannot accurately measure quality of life across all age groups. Consequently, we have developed three questionnaires; one for children aged 8 to 12 years (primary school), one for adolescents aged 13 to 17 years (secondary school) and one for adults 18 years and older.

Moreover, when measuring HRQL in children it is important to take age, maturity and cognitive development into account in the development of the questionnaire <sup>11</sup>. In order to ensure age-appropriateness, we included food allergic children in the development process of the questionnaire. In addition, answer categories were illustrated by faces (smileys) which is appropriate for the cognitive development of the child. Finally, a consultant for sick children reviewed the child questionnaire for clarity and ease of use. Another important issue was to decide the lower limit of age at which a child is able to report on their own quality of life in the form of a self-completed questionnaire. Although the understanding of HRQL is determined by the age, maturity and cognitive development of the child, it has been reported that children 8 years and older are able to understand questions about their HRQL and to give reliable and valid answers <sup>12</sup>.

When looking at the content of the final questionnaires for the different age groups, it was striking to see that a considerable part of the items showed overlap. Thus, although we separately interviewed food allergic children, adolescents and adults and generated many age-specific items, there are apparently general food allergy items that are important in all age groups. Moreover, we found that the three most important items, determined during the item reduction phase, were the same for all the three age groups: 'Always be alert as to what you are eating', 'The ingredients of a product change', 'Able to eat fewer products'. Although there was overlap of items, important age-specific items emerged in each questionnaire as well. Examples of items specific for children were: 'Don't get anything when someone is giving treats at school', 'Concerned that you will never get rid of your food allergy', 'Not knowing how things taste which you can't eat' and 'Feel disappointed because you have a food allergy'. Examples of items specific for adolescents were: 'Refuse treats at school or work', 'Carrying an EpiPen' and 'During social activities your food allergy is not taken into account'. Examples of items specific for adults were: 'Eating out less often', 'Feel you are being a nuisance because you have a food allergy when eating out', 'Sometimes frustrate people when they are making an effort to accommodate your food allergy' and 'People underestimate your problems caused by food allergy'. Finally, the layout of the child questionnaires

differs significantly from the other two questionnaires since the answer categories in the child questionnaire are illustrated by smileys. Therefore, in conclusion, we think it is important to have three separate questionnaires for three different age groups.

## **The importance of including patients in the item generation and item reduction**

Developing a valid and robust questionnaire is not just putting some questions together<sup>13</sup>. Usually the development of a questionnaire starts with item generation<sup>14</sup>. During the item generation all kinds of possible items for the new questionnaire are assembled. One source or more different sources may be used such as patients, clinicians and the literature<sup>15</sup>. Since a disease-specific HRQL questionnaire intends to measure the impact of a disease as perceived by the patient, it has been argued that patients are the most important source for generating items, because they generate the items that are really a problem as perceived by the patients themselves. Moreover, it is important to include patients that are representative for the patients in whom the final questionnaire will be used<sup>11</sup>.

The item generation is usually followed by the item reduction in which the items are reduced to a manageable number for inclusion in the questionnaire. Different methods may be used for the reduction of items, of which the clinical impact method and the psychometric approach (factor analysis) are the most frequently used methods<sup>16</sup>. In the development of the FAQLQs we used the clinical impact method which reveals items that are clinically most important as perceived by food allergic patients. This is in contrast to the method of selecting items based on mathematical linkage between items by performing factor analyses in which items with a low loading on a factor are removed. The latter method has the potential drawback that it may result in excluding items with a high clinical impact<sup>16</sup>. Juniper et al., who also used the clinical impact method for developing the Asthma Quality of Life Questionnaire (AQLQ), showed that the three items of the greatest importance to patients with asthma would have been excluded from the AQLQ if they had used the psychometric approach (factor analysis)<sup>16</sup>. A possible drawback of selecting items based on their clinical importance may be that, when you perform factor analysis on these most important items, the allocation of items into domains does not always make intuitive sense. Therefore, in the development of the FAQLQs we used the clinical impact method for selecting items. Subsequently, the allocation of items into domains was based on factor analysis supplemented by face validity determined by an expert panel.

## Cross-sectional validation with the Food Allergy Independent Measure (FAIM)

Once the items are selected for the new questionnaire, it is important to determine whether the individual questions and the total questionnaire measure the things that it are intended to measure, also known as validity. As discussed in the **chapters 3, 4, 5 and 8**, no ‘gold standard’ HRQL measure exists to which a new HRQL questionnaire could be compared with to investigate validity, which is known as ‘criterion’ validity in this context <sup>17</sup>. Therefore, construct validity is the best achievable form of validity, which is ascertained by calculating the correlation between the HRQL questionnaire and an independent measure. An independent measure is usually viewed as an important determinant of HRQL, but it is not itself a HRQL item. In addition, it is often an indication of the severity of the disease and it may at the same time be a target for intervention, such as FEV1 in asthma. However, since symptoms occur only upon exposure in anaphylactic disorders, no objective measurement of the extent or ongoing severity of disease exists with which to correlate the new HRQL questionnaire <sup>18</sup>.

Therefore, we used the Food Allergy Independent Measure (FAIM) to investigate the construct validity of the FAQLQs, which is based on the concept first described by Oude Elberink et al <sup>19</sup>. The FAIM was developed for this research and includes four Expectation of Outcome (EO) questions and two other independent measure questions. Two of these EO questions were adapted from similar questions previously developed for the validation of the Vespil Allergy Quality of Life (VQLQ) questionnaire (i.e. ‘chance of having a severe reaction when stung’ and ‘chance of dying when accidentally stung’) <sup>19</sup> and the validation of the Food Allergy Quality of Life-Parental Burden (FAQL-BP) questionnaire (i.e. ‘chance of having a severe reaction when accidentally exposed’ and ‘chance of dying when accidentally exposed’) <sup>9</sup>. These two EO questions have successfully been implemented to validate the VQLQ and the FAQL-PB questionnaire <sup>9;19;20</sup>. For the validation of the FAQLQs we have developed two additional food allergy specific EO questions (i.e. ‘chance of accidental exposure’ and ‘chance of not acting effectively when accidentally exposed’) and two additional independent measure questions. The EO questions are based on the perceived expectation of patients of what will happen following exposure which is likely to be a driving force of quality of life <sup>18</sup>. The additional independent measure questions are based on the same principle and ask about the perceived number of foods one needs to avoid and perceived impact on social life.

In addition to the use of the FAIM for the investigation of the validity of the FAQLQs and the individual items of the FAQLQs, we also used the correlation between the individual FAQLQ items and the FAIM for the selection of items for the final questionnaire. That is, if an item of the FAQLQ did not correlate with any of the FAIM questions, than it was excluded from the questionnaire. Our starting point was to include only items that are perceived as important by the patients

themselves (i.e. high overall importance (OI)) which measure that part of quality of life that is affected by food allergy (i.e. correlation with FAIM). If an item does not correlate with any of the FAIM questions, then it should not be in the questionnaire in the first place, whether or not it fits well in the scale or domains. Therefore we investigated the domain structure (factor analysis) and the internal consistency after the investigation of the construct validity. This was also the methodology used in previous studies which produced the VQLQ <sup>19</sup>.

## Should we use generic HRQL questionnaires in food allergy?

In **chapter 7** we presented the results of the study on HRQL of food allergic patients measured with generic and disease-specific questionnaires. Measurement of generic and disease-specific HRQL in the same group of food allergic patients has never been done before. The aims of this study were to compare generic HRQL of food allergic patients with the general population and other diseases (asthma, irritable bowel syndrome (IBS), diabetes mellitus type I (DM) and rheumatoid arthritis (RA)) and to compare HRQL of food allergic patients as measured with generic and disease-specific questionnaires. We found that food allergic children reported the least impact of food allergy on generic HRQL, which was even better than in children in the general population in some respects. Food allergic adolescents and adults reported overall poorer generic HRQL than the general population. In addition, we found that the generic HRQL impact of food allergy is intermediate in magnitude between DM and asthma, IBS and RA. Moreover, we found very high ceiling effects for some generic scales, which may indicate that generic HRQL questionnaires are not sufficiently sensitive to measure disease-specific clinically important impairments in food allergy. Thus, generic HRQL questionnaires may be useful to compare the impact of food allergy on HRQL with the general population and other chronic diseases. However, for measuring disease-specific effects in food allergic patients, it is preferable to use disease-specific questionnaires.

Although we found that food allergy has a greater impact on generic HRQL than DM, it is remarkable that this is not reflected in the attitudes of governments and societies. For example, if you search in 'Google' for the word 'food allergy', then you get 1,960,000 hits within 0.13 seconds. If you search in 'Google' for the word 'diabetes mellitus', then you get 7,080,000 hits within 0.06 seconds. Although the prevalence of both diseases differ somewhat, approximately 2% for food allergy and approximately 4% for DM <sup>21;22</sup>, societal attention for these diseases may be out of proportion to each other. Further comparative studies between food allergy, DM and other chronic diseases will show if the similar differences in HRQL impact are seen as in our study.



## Availability of valid disease-specific HRQL questionnaires for food allergic patients

In **chapter 8**, we present a review on how HRQL can be measured in food allergy and we reviewed recent findings on how food allergy might impact HRQL. We found that in addition to the more familiar burdens of having a food allergy, the psycho-social impact of food allergy and information gaps concerning food allergy have received much attention in the recent literature. In addition, we described that the FAQLQs, which we have developed, have become available recently. These are reliable and valid disease-specific HRQL questionnaires to measure the impact of food allergy on HRQL in patients of all ages. The assessment of HRQL could be used by clinicians to get insight in the specific problems patients have to face and HRQL measurements may be used to measure the effects of an intervention on the patient's quality of life. One of the key messages of **chapter 8** was that HRQL is the only available measure that reflects the ongoing severity of food allergy, since no objective disease parameters are available.

## Summary of main findings

The main findings of this thesis were as follows:

- 1) At the beginning of this study (June 2005), there was a need for valid HRQL questionnaires for food allergic patients
- 2) Disease-specific HRQL questionnaires have been developed for children (8-12 years), adolescents (13-17 years) and adults (18 years and older) with food allergy.
- 3) These questionnaires showed good validity and reliability.
- 4) For measuring disease-specific impact of food allergy on HRQL, disease-specific questionnaires may be more useful than generic HRQL questionnaires.
- 5) The impact of food allergy on HRQL is greater than the impact of diabetes mellitus, but less than the impact of asthma, IBS and rheumatic arthritis as measured with generic HRQL questionnaires.

## Recommendations for future study

Following the findings discussed in this thesis, there are a number of studies of interest for the future:

- *Longitudinal validation.* In order to investigate if the FAQLQs are able to measure differences over time, the longitudinal validity of the questionnaires should be investigated. The longitudinal validity could be investigated by administering

the FAQLQ and the FAIM to food allergic patients in whom HRQL is expected to change because of diagnostic and/or therapeutic interventions. The questionnaires should be administered before and a few months after the intervention, so that patients could become accustomed to their new health state. Preliminary data have shown that for some domains HRQL is already significantly improved two months after a diagnostic intervention (i.e. double-blind placebo-controlled food challenge) (DunnGalvin et al., unpublished data, December 2008). Changes in the average score of the FAQLQ are then correlated to changes in the FAIM, comparing values before and after the intervention described. Good correlation between the FAQLQ and FAIM scores validate the instrument longitudinally and simultaneously demonstrate the impact on quality of life of the intervention used.

- *Comparison of the children's FAQLQ-CF scores with their parents' FAQLQ-PF scores.* As discussed earlier, children and parents may differ in their views and judgements concerning HRQL<sup>23</sup>, and it would thus be interesting to investigate and compare the scores of children on the FAQLQ-CF with the scores of their parents on the FAQLQ-PF.

- *Determination of the Minimal Importance Difference (MID).* The MID is the smallest difference in score which patients perceive as beneficial and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management. The MID of HRQL questionnaires with a 7-point scale is usually approximately 0.5<sup>24</sup>. It is important to determine the MID of the FAQLQs, because it gives clinicians and researchers insight into whether a change in the FAQLQ score, for example before and after an intervention, is also a clinically important change.

- *Comparison of informed versus blind administration of follow-up questionnaires.* It would be interesting to investigate if there is a difference in scoring on a follow-up questionnaire when the patients are shown their previous answers (i.e. informed) with the scores generated when there are not shown their previous answers (i.e. blind). It has been suggested that when letting patients see their previous responses, the validity of HRQL questionnaires in clinical trials can be improved<sup>25</sup>. However, when the follow-up measurement was more than three months later, the results of the blind and informed questionnaire showed little difference<sup>26</sup>. These studies were all performed in adults. Therefore, it would be interesting to see if the same is true for children and in food allergic patients.

- *Validation of FAQLQ in other countries.* Before the FAQLQs can be used in other languages and cultures, the questionnaires should be cross-culturally validated in the new language or culture<sup>27</sup>. Forward and backward translation may be used in order to check content comparability. Cross-sectional validation in the new language and cultural setting allows for the assessment of the performance of individual items in that language and culture. Good cross-sectional correlation coefficients indicate validity for that particular language setting. Low correlation coefficients may be encountered if the translation is inaccurate or if the item does not appear to be a problem in the new cultural context. Following successful cross-sectional validation in the new language and cultural setting, the questionnaire could be

incorporation into a longitudinal study in the new language as indicated above.

- *Combine HRQL outcomes with economic measurements.* It would be interesting to combine HRQL outcomes measured with the FAQLQs with economic outcomes measured with the economic questionnaire for food allergy which was also developed within EuroPrevall<sup>28,29</sup>. Interesting questions such as: “Is the social impact of food allergy related to the economic impact of food allergy?” could be investigated. In addition, it would be interesting to investigate if the FAQLQs could be used to calculate Quality-Adjusted Life Years (QALYs). Lamers et al.<sup>30</sup> showed that it is feasible to convert data collected with a disease-specific questionnaire into preferences, which can be used to calculate QALYs. A QALY measures the amount of healthy years gained by a particular health care intervention. QALYs could be used in cost-utility analysis to calculate the ratio of costs to QALYs saved for a particular health care intervention.

- *Combine HRQL outcomes with epidemiological data.* Finally, one of the major aims of the EuroPrevall project is to assess the societal impact of food allergies<sup>31</sup>. In order to realise this, it is important to combine the information from studies on HRQL with epidemiological data on prevalence. This will ultimately give some indication of the magnitude of the societal impact of food allergy in Europe.

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